DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES
April 17, 2015

The Executive Formulary Committee convened on Friday, April 17, 2015 in Room 111 - ASH Building 582. The meeting was called to order by Dr. Race, Acting Chair at 9:43 a.m.

Phillip Balfanz, M.D.	√	Valerie Kipfer, MSN, RN (non-voting)	Absent
Mary Bowers RN, BSN	Absent	Lilani Muthali, M.D. (non-voting)	√
Catherine Hall, Pharm.D.	√	Nina Muse, M.D. (Acting Medical Director)	√
Jeanna Heidel, Pharm.D.	√	Jay Norwood, MSN, RN (non-voting)	Absent
Marla Knight, Pharm.D., CGP, FASCP	Absent	Peggy Perry (non-voting)	Absent
Jeff Matthews, M.D. (via phone)	√	Scott Schalchlin (non-voting)	Absent
Connie Millhollon, RN	Absent	Lauren Lacefield Lewis (non-voting)	Absent
Kenda Pittman, Pharm.D.	√	Kerry Raymond (non-voting)	Absent
George Race, M.D.	√	Vacant Center Position	
Ann L. Richards, Pharm.D.	√	Vacant Center Position	
Archie Smith, M.D.	√	Vacant DADS Physician	
Jennifer Wright, M.D.	Absent		

Guests Present: Kristen Backe, Pharm.D., Resident, ASH; Cassandra Sanchez, Pharm.D. Resident, SASH; Robert L. Ward, D.O., Kerrville State Hospital

Introduction and Other Information

The Hospital Section recently formed a Medical Executive Committee. During their last meeting, the Committee recommended that the Hospital Section add another hospital psychiatrist to the Executive Formulary Committee. The recommendation was approved by Ms. Peggy Perry and Dr. Race was appointed to the Committee. Dr. Race previously served on the Executive Formulary Committee in his prior role with the Hospital Section. With Dr. Wright's absence, Dr. Race served as the Acting Chair for the meeting.

Dr. Backe, Dr. Sanchez and Dr. Ward were introduced as guests.

Approval of Minutes of January 30, 2015

On a motion of Dr. Heidel, seconded by Dr. Balfanz, the minutes of the January 30th meeting were approved as previously distributed.

Conflict of Interest

Dr. Race completed his disclosure statement and did not report any conflict of interest. None of the Committee members present reported any conflicts of interest.

Issues from the Medical Executive Committee

Dr. Richards noted that the Medical Executive Committee is a new committee that was formed to address clinical issues in the State Hospitals. The Committee is led by Dr. Parsons and includes a few other clinical directors. At their last meeting, the Medical Executive Committee discussed medication errors and the lack of reporting throughout their respective facilities. The Medical Executive Committee suggested reviewing their facility data for medication errors and considering a system-wide medication error education program to encourage and evaluate medication errors.

Adverse Drug Reaction Reports

The Executive Formulary Committee discussed one adverse drug reaction report that was received from the field.

> This case involves a 35 year old male with a seizure disorder that is not adequately controlled with maximum doses of topiramate (Topamax®) and zonisamide (Zonegran®). On February 11, 2015, lamotrigine (Lamictal®) 50 mg daily for 7 days was added to his medication regimen. The addition was the beginning of a planned titration to the maximum dose of lamotrigine. He received the initial dose in the evening of February 11th. In the morning of February 12th, a red, raised rash was noticeable around his neck and behind his ears. Since no other cause for the rash could be identified and the concern for the boxed warning regarding serious skin rashes with lamotrigine, the lamotrigine was immediately discontinued. He was kept in the infirmary overnight to observe the rash. The rash resolved within 72 hours.

The Committee noted that this case did not follow the manufacturer's recommended titration schedule. Committee members reported that they have seen orders for lamotrigine initiation that do not follow the recommended dosing schedule. One facility reports not honoring these orders and getting them rewritten to follow the manufacturer's recommended dosing schedule.

The Committee made two recommendations based on this case. The first recommendation was a reminder that if lamotrigine did induce a rash, that the medical record as well as other medication related forms, be marked with a lamotrigine allergy in order to prevent future exposure. The second recommendation was to remind the facilities about following the recommended dose titration when initiating lamotrigine.

New Drug Applications

The Committee did not receive any new drug applications.

Drug Deletions

No drugs were being considered for deletion at this time.

New Dosage Strengths

The Committee did not consider any dosage strength addition to the Formulary.

Quetiapine (Seroquel®, Seroquel® XR) Purchases

Dr. Richards reviewed the State Hospital purchases and returns of Seroquel® and Seroquel® XR from January through March. The hospitals did not make any purchases for these products during this time frame.

Psychotropic Audit Criteria – Lab Summary

With the recent update of the psychotropic audit criteria for mood stabilizers, Austin State Hospital updated their "Psychotropic Monitoring Guidelines" lab summary. See Attachment A. This document provides a summary of labs required for psychotropic monitoring. In the past, this document had been distributed to the field. The Committee recommended that this document be posted on our website.

Psychotropic Audit Criteria & Guidelines - Antidepressants

The Antidepressant Audit Criteria and Guidelines have not been reviewed.

Psychotropic Audit Criteria & Guidelines – Chemical Dependence Adjunct

The Chemical Dependence Adjunct Audit Criteria and Guidelines have not been developed.

Hydroxyzine – QTc Interval

The European Medicine Agency Pharmacovigilance Risk Assessment Committee (PRAC) completed a review of medicines containing hydroxyzine. The following are the findings of PRAC:

> "The PRAC considered that hydroxyzine was associated with a small but definite risk of QT interval prolongation and torsade de pointes (alterations in the electrical activity of the heart that can lead to abnormal heart rhythms and cardiac arrest). Based on the assessed data, the risk did not differ between indications, and the Committee recommended that hydroxyzine could continue to be used provided that measures to minimize the risk of problems with heart rhythm were taken.
>
> These measures include using the medicine at the lowest effective dose for as short a time as possible. Use is not recommended in the elderly. The maximum daily dose should be no more than 100 mg in adults (50 mg in elderly if use cannot be avoided), and 2 mg per kg body weight where used in children up to 40 kg weight. Use must be avoided in patients who already have risk factors for heart rhythm disturbances or are taking other medicines that increase the risk of QT prolongation. Care is also needed in patients taking medicines that slow the heart rate or decrease the level of potassium in the blood, as these also increase the risk of problems with heart rhythm.
>
> The PRAC recommendation follows a detailed review of the available evidence, which included published studies and data from regular safety monitoring, as well as consultation with experts in the treatment of children and the elderly. PRAC confirmed the known possibility of QT interval prolongation and torsade de pointes with hydroxyzine, and noted that such events were most likely to occur in patients who had risk factors. The risk can therefore be decreased by restricting hydroxyzine use in those most at risk of heart rhythm problems and reducing exposure to the medicine. The Committee recommended further study and monitoring to ensure that these measures were effective. The product information should be updated accordingly."

CredibleMeds™ (www.crediblemeds.org) is a website that lists medications that prolong QT interval. CredibleMeds™ ranks hydroxyzine as "Conditional Risk of TdP (Torsade de Pointes)." "Conditional Risk of TdP means substantial evidence supports the conclusion that these drugs are associated with a risk of TdP BUT only under certain conditions (e.g. excessive dose, hypokalemia, congenital long QT or by causing a drug-drug interaction that results in excessive QT interval prolongation)."

The DADS/DSHS Drug Formulary currently lists the following dosing information regarding hydroxyzine:

- Based on survey data from practitioners treating this population within our agency, the following behavioral emergency doses:
    - Children < 12 years old – hydroxyzine IM 25 – 50 mg every 4 to 6 hours with a max dose of 150 mg/day.
    - Adolescent 12 year old to < 18 years old – hydroxyzine IM 50-100 mg every 4 to 6 hours with a max dose of 200 mg/day
- Adult treatment of behavioral emergencies – hydroxyzine IM 100 mg every 1 hour with a max dose of 400 mg/day
- Hypnotic
    - Under 65 years old – 400 mg/day
    - 65 years old and older – 300 mg/dayn
    - Child 3-6 years old – 25 mg/day (based on literature)
    - Child 6-12 years old – 50 mg/day (based on literature)
    - Adolescent > 12 years old but less than 18 years old – 100 mg (based on literature)

After the information from the European Medicine Agency was released, Austin State Hospital developed and initiated an audit for hydroxyzine to determine the appropriate use and the impact on the QT interval. Currently, ASH is in the process of evaluating the data.

As a comparison, Dr. Balfanz noted that a pediatric organization does not recommend obtaining an EKG with the use of stimulants based on experience. In the past, clinicians did obtain EKGs with stimulants but did not find anything. Now, clinicians are obtaining a good medical and family history regarding cardiac issues.

After reviewing and discussing this information, the Committee recommended the following:

- The information be shared with the facilities to educate the staff about the potential for QT prolongation with hydroxyzine
- Using the ASH's hydroxyzine drug use evaluation (DUE), it was recommended that each facility complete this DUE in order to determine the appropriate use and impact on the QT interval. The data would be submitted and evaluated for possible changes in the use of hydroxyzine.
- The Medical Executive Committee for the Hospital Section considers adding an EKG (for obtaining a strip to determine the QT interval) as a routine admission requirement since numerous drugs affect the QT interval.

The data obtained from the DUEs will be presented at the next meeting for consideration regarding the status of hydroxyzine.

Drug Formulary Sectional Review- Psychotropic Agents

Dr. Hall provided the review on the agents in the Psychotropic section. See Attachment B. Based on her review, Dr. Hall made the following recommendations:

- Delete the following from the Formulary due to lack of purchases for the past year:

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Amoxapine	Asendin®	Tablet: 25 mg, 50 mg, 100 mg, 150 mg	None
Maprotiline	Ludiomil®	Tablet: 25 mg, 50 mg, 75 mg	None
Trimipramine	Surmontil®	Capsule 25 mg, 50 mg, 100 mg	None

- Change the name of the "Miscellaneous Agents" under the Antidepressant section to "Miscellaneous

Antidepressant Agents"

- Add oxcarbazepine (Trileptal®), topiramate (Topamax®) to the Mood Stabilizer section as the new mood stabilizer audit criteria and guidelines list at least one form of bipolar disorder as an indication for these agents
- Change valproate to valproic acid in the mood stabilizers section
- Merge the "Anxiolytics and Hypnotics" section with the "Benzodiazepines" subsection under "Psychotropic Agents."
    - Change the name of this section to "Benzodiazepine anxiolytics and hypnotics"
    - Add midazolam (Versed®) to this section
- Delete the "Miscellaneous Psychotropic Agents" subsection. As a result of this deletion:
    - Add a new subsection "Miscellaneous Anxiolytics and Hypnotics." Add the following to this subsection:
        - Diphenhydramine (Benadryl®)
        - Trazodone (Desyrel®)
        - Zaleplon (Sonata®)
        - Zolpidem (Ambien®)
        - Buspirone (BuSpar®)
        - Hydroxyzine (Atarax®, Vistaril®)
        - Prazosin (Minipress®)
    - Add a new subsection "Other ADHD Agents" under the "Stimulants" section. Add the following to this subsection
        - Guanfacine (Tenex®)
        - Clonidine (Catapres®)
    - Delete naloxone (Narcan®) as it is in the "Antidotes/Deterrents/Poison Control Agents"
    - Delete naltrexone (ReVia®) as it is in the "Chemical Dependency Adjuncts"
- Delete the following discontinued items:

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Clorazepate	Tranxene®	Tablet, sustained release: 11.25 mg, 22.5 mg	Tablet: 3.75 mg, 7.5 mg, 15 mg
Diazepam	Valium®	Gel, rectal: 5 mg, 15 mg	Gel, rectal: 2.5 mg, 10 mg, 20 mg Injection: 5 mg/ml Solution, oral: 1 mg/ml, 5 mg/ml Tablet: 2 mg, 5 mg, 10 mg
Paroxetine	Paxil®	Tablet, controlled release: 50 mg	Suspension: 10 mg/5 ml Tablet: 10 mg, 20 mg, 30 mg, 40 mg Tablet, controlled release: 12.5 mg, 25 mg, 37.5 mg
Thioridazine	Mellaril®	Tablet: 15 mg, 150 mg, 200 mg	Tablet: 10 mg, 25 mg, 50 mg, 100 mg
Thiothixene	Navane®	Capsule: 20 mg	Capsule: 1 mg, 2 mg, 5 mg, 10 mg
Hydroxyzine	Atarax®, Vistaril®	Tablet: 100 mg	Capsule: 25 mg, 50 mg, 100 mg Injection: 25 mg/ml, 50 mg/ml Suspension: 25 mg/5 ml Syrup: 10 mg/5 ml Tablet: 10 mg, 25 mg, 50 mg

On a motion of Dr. Heidel, seconded by Dr. Pittman, the recommended changes to the psychotropic section were approved. Feedback from the field will be obtained on the recommendation to delete amoxapine, maprotiline and trimipramine since these items are currently on the market. Feedback will not be obtained on the deletion of products no longer available.

Dr. Hall provided a brief overview on the use of antipsychotic polypharmacy based on the following meta-analysis: Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S. Antipsychotic Combinations vs Monotherapy in Schizophrenia; A Meta-analysis of Randomized Controlled Trials. *Schizophr Bull*. 2009;35(2):443-547.

- Searched register of Cochrane Schizophrenia Group (CSG) for published or unpublished Randomized Controlled Trials (RCTs) that compared antipsychotic monotherapy to the combination of that same antipsychotic plus another one in patients with schizophrenia or related disorders
- Identified 19 studies (1216 participants)
    - Average trial duration = 12.1 $\pm$ 11.3 weeks
    - Average age = 33.4 $\pm$ 5.1 years
    - 62.3% male
    - 88.3% inpatients
        - 15 studies in patients with chronic illness (n = 1054), 4 studies in patients with acute exacerbation (n=162)
    - 98.7% patients suffered from schizophrenia
    - Clozapine used most (N=11, n=542) followed by chlorpromazine (N = 6, n = 375), then risperidone (N = 6, n = 188)
        - Pimozide, thioridazine, fluphenazine, trifluoperazine, reserpine, haloperidol, olanzapine, levomepromazine
- Sensitivity Analyzes
    - (1) double-blind vs single-blind/open label, (2) Chinese vs non-Chinese studies, (3) acutely exacerbated vs chronically ill, (4) combined initiation vs delayed augmentation after nonresponse, (5) comparative vs reduced antipsychotic doses in co-treatment arm, (6) < 10 weeks vs $\geq$ 10 weeks, (7) clozapine vs non-clozapine combinations, (8) co-treatment with 2 first generation antipsychotics compared with 1 first generation antipsychotic; co-treatment with 2 second generation antipsychotics vs 1 second generation antipsychotic; co-treatment with an first generation antipsychotic plus second generation antipsychotic compared with either a first generation antipsychotic or second generation antipsychotic
    - Most confirmed superiority for antipsychotic co-treatment vs monotherapy for lack of study-specific defined inefficacy.
        - Five efficacy moderators emerged
            - Combinations with clozapine
            - Second generation antipsychotic plus first generation antipsychotic
            - Trial duration > 10 weeks
            - Concurrent polypharmacy initiation
            - Chinese trials (7/19)

The combinations with clozapine and the combination of a second generation antipsychotic with a first generation antipsychotic appeared more efficacious than antipsychotic monotherapy. When one eliminates the Chinese trials, then polypharmacy no longer appears superior to monotherapy.

Dr. Hall completed a review of the following trial: Essock SM, Schooler NR, Stroup TS, et al. Effectiveness of Switching From Antipsychotic Polypharmacy to Monotherapy. *Am J Psych*. 2011; 168:702-708.

- 15 study sites in NIMH's Schizophrenia Trials Network, 5 sites in Connecticut's public mental health system

- 127 outpatients with schizophrenia or schizoaffective disorder currently taking 2 antipsychotics (plasma levels) were randomized to stay on polypharmacy or switch to monotherapy
- Excluded
    - patients with severe symptoms or side effects who needed immediate medication change
    - In last 3 months
        - 1 night in hospital
        - crisis intervention services
        - psych ER
    - patients in skilled nursing facility as result of physical condition or disability
    - pending criminal charges
    - pregnant/breast-feeding
    - 3 or more daily antipsychotics

	Stay on Poly (N = 62)		**Switch** (N = 65)		**Analysis**
	N	%	N	%	p
Male	34	55	50	77	0.01
Caucasian	27	44	42	65	0.02
Latino	9	15	5	8	0.23
TD	15	25	10	15	0.18
EPS	18	30	19	29	0.97
	Mean	SD	Mean	SD	p
Baseline daily dose (mg haloperidol equivalent)	6.1	3.4	7.2	5.5	0.06
Baseline daily dose (mg chlorpromazine equivalent)	325.8	184.4	387.8	296.7	0.06
PANSS score	72.4	14.3	70.9	14.5	0.57
BMI	31.9	7.7	31.4	7.5	0.69
ASEX score	17.2	6.0	18.0	6.2	0.47

- Baseline polypharmacy combinations
    - Quetiapine + risperidone (N = 25)
    - quetiapine + first generation antipsychotic (N = 25)
    - risperidone + first generation antipsychotic (N = 23)
    - olanzapine + first generation antipsychotic (N = 22)
    - ziprasidone + first generation antipsychotic (N = 12)
    - aripiprazole + quetiapine (N = 11)
    - olanzapine + risperidone (N = 10)
    - other combinations totaling $\leq$ 10 pts (N = 39)

At the end of six months, for those patients that were switched to monotherapy, approximately 69% were able to stay on monotherapy and not be switched back to polypharmacy. For those that were on polypharmacy, approximately 86% remained on polypharmacy at the six month time period. Blinded raters completed PANSS assessment on the patients. The data indicates that the raters could not tell any difference between the two groups.

A review of antipsychotic plasma levels and their usefulness was provided by Dr. Hall. The AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry; Update 2011 gave the following antipsychotics a Level I (strongly recommended) recommendation:

- clozapine
- haloperidol
- fluphenazine
- olanzapine
- perphenazine
- amisulpride (not available in U.S.)

After reviewing the information on antipsychotic polypharmacy and plasma levels, Dr. Hall presented Dr. Stahl's guidelines for polypharmacy based on the following: Stahl SM. Emerging guidelines for the use of antipsychotic polypharmacy. *Rev Psiquiatr Salud Ment (Barc.)*. 2013;6(3): 97-100.

- "The paradigm for treating schizophrenia is shifting from discouraging all uses of polypharmacy/combinations, to determining instead who should get polypharmacy/combinations."
- The journey from antipsychotic monotherapy to antipsychotic polypharmacy: a dozen suggestions
    - $\geq$ 2 consecutive antipsychotic monotherapies at appropriate doses for appropriate times
    - Clozapine
    - Try another antipsychotic, and then get drug levels to see if pharmacokinetic versus pharmacodynamic failure
    - If pharmacokinetic failure, raise dose (or convert to depot) and repeat blood levels until therapeutic
    - If pharmacodynamic failure, treat up to 1 year as some patients will respond late
    - Consider another diagnosis
    - Consider surreptitious drug abuse
    - Consider adding a mood stabilizer if any mood component
    - Define therapeutic target, try polypharmacy for (possibly) treatable symptoms
        - Positive symptoms
        - Impulsivity
        - Hostility
        - Violence (impulsive or psychotic)
        - Self-harm (psychotic, compulsive behavior that has become a habit)
    - If 2 antipsychotics given, monitor side effects, blood levels of both
    - Stop second antipsychotic if no improvement
    - If improvement, document specific target behaviors improved
        - After several months, consider discontinuation trial of one agent
        - Relapse might point to need for long term polypharmacy

Dr. Sanchez provided a brief review of the following drugs. See Attachment C.

- Levomilnacipran (Fetzima®) - nonformulary
- Desvenlafaxine (Pristiq®) - nonformulary
- Vilazodone (Viibryd®) - nonformulary
- Vortioxetine (Brintellix®) - nonformulary
- Iloperidone (Fanapt®)
- Asenapine (Saphris®)
- Lurasidone (Latuda®)

After reviewing the information, the Committee recommended that guidelines for obtaining antipsychotic blood levels be developed. In addition, these guidelines should include costs. Dr. Hall volunteered to develop these guidelines.

Supported Living Centers – Anticonvulsant Use

At the October's meeting, it was noted that many individuals at the Supported Living Centers are on three or more anticonvulsants for the treatment of seizure disorders. It was suggested that this data be brought back to the Committee for discussion. The following data was obtained by Dr. Knight:

	Based on number of AEDS			Based on Census		
Campus	3 or more AEDs	# on AEDs	Percentage	Census	% 3 or more	% on AEDs
ABSSLC	45	175	25.7%	334	13.5%	52.4%
AUSSLC	31	107	29%	213	14.6%	50.2%
BSSLC	29	117	24.8%	284	10.2%	41.2%
CCSSLC	29	118	24.6%	225	12.9%	52.4%
DSSLC	63	235	26.8%	456	13.8%	51.5%
EPSSLC	16	63	25.4%	105	15.2%	60%
LBSSLC	28	92	30.4%	201	13.9%	45.8%
LFSSLC	39	139	28.1%	319	12.2%	43.6%
MSSLC	24	112	21.4%	264	9.1%	42.4%
RSSLC	37	121	30.6%	330	11.2%	36.7%
SaGSSLC	7	65	10.8%	210	3.3%	31%
SASSLC	23	96	24%	230	10%	41.7%
Total	371	1440	25.8%	3171	11.7%	45.4%

The Committee discussed whether or not there is an acceptable number of seizures before a medication change should be made. The Committee noted that seizure treatment needs to be individualized and medication changes should be based on the frequency of the seizures, the length and type of seizures. It was noted that even though phenobarbital is rarely started in practice, if a patient was on phenytoin (Dilantin®) and phenobarbital and didn't have seizures, the medication would probably not be changed. In addition, the Committee thought that San Angelo State Supported Living Center had the lowest percentage of individuals on three or more anticonvulsants due to the population that is served at that facility.

It was reported that the State Supported Living Centers still had individuals with seizures that are not controlled, had incidents of sudden death with seizures, aspiration with seizures, and falls and fractures with seizures. Neurologists see individuals with seizures at least every two years but most are seen annually and more often as clinically needed. In some cases, the seizures are challenging to treat and more and more anticonvulsants are being added to the medication regimen in order to decrease the number/length of seizures.

Formulary Work Request

Currently, Ms. Debra Gregg, Assistant Pharmacy Director for the San Antonio State Hospital maintains the Drug Formulary. In working with the Formulary, she has noticed that trade names are not current as well as lack of consistency between tables and the drug listing. Ms. Gregg requested permission to update the Formulary without first going through the Committee. In addition, Ms. Gregg requested that source documents (e.g., psychotropic audit criteria) be identified so that the Formulary can match the source document. The Committee suggested thatold trade names continue to be included in the Formulary in order to make searching the document easier. On a motion of Dr. Heidel, seconded by Dr. Smith, this recommendation was approved.

FDA Drug Safety Communications

The FDA has issued the following safety communication that may have impact on our facilities.

> The FDA is requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications. The FDA is also requiring these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. The FDA cautions that prescription testosterone products are approved only for men

who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone. Based on the available evidence from studies and expert input from an FDA Advisory Committee meeting, the FDA has concluded that there is a possible increased cardiovascular risk associated with testosterone use. These studies included aging men treated with testosterone. Some studies reported an increased risk of heart attack, stroke, or death associated with testosterone treatment, while others did not.

The FDA is warning that the prescription smoking cessation medicine varenicline (Chantix®) can change the way people react to alcohol. Interactions between alcohol and varenicline have resulted in some patients experiencing increased intoxicating effects of alcohol, sometimes associated with aggressive behavior and/or amnesia. In addition, rare accounts of seizures in patients treated with varenicline have been reported. The FDA has approved changes to the varenicline label to warn about these risks. Healthcare professionals should weigh the potential risk of seizures against the potential benefits before prescribing varenicline in patients with a history of seizures or other factors that can lower the seizure threshold. Advise patients to immediately stop taking varenicline if they develop agitation, hostility, aggressive behavior, depressed mood, or changes in behavior or thinking that are not typical for them, or if they develop suicidal ideation or behavior.

The FDA has concluded a review of a study undertaken to determine the cause of elevated levels of the injectable schizophrenia drug olanzapine pamoate (Zyprexa® Relprevv™) in two patients who died. The study results were inconclusive. The FDA is unable to exclude the possibility that the deaths were caused by rapid, but delayed, entry of the drug into the bloodstream following intramuscular injection. The study suggested that much of the drug level increase could have occurred after death, a finding that could explain the extremely high blood levels found in the two patients who died 3 to 4 days after receiving injections of appropriate doses of olanzapine pamoate. On the basis of all of the information reviewed (refer to the Drug Safety Communication for a full data summary), the FDA is not recommending any changes to the current prescribing or use of olanzapine pamoate injection at this time.

The FDA is warning that serious slowing of the heart rate can occur when the antiarrhythmic drug amiodarone is taken together with either the hepatitis C drug ledipasvir/sofosbuvir (Harvoni®) or with sofosbuvir (Sovaldi®) taken in combination with another direct acting antiviral for the treatment of hepatitis C infection. The FDA is adding information about serious slowing of the heart rate, known as symptomatic bradycardia, to the Harvoni® and Sovaldi® labels. The FDA is recommending that health care professionals should not prescribe either Harvoni® or Sovaldi® combined with another direct acting antiviral, such as the investigational drug daclatasvir or simeprevir (Olysio®), with amiodarone.

Hepatitis C Treatment Guidelines

Dr. Muse joined the meeting to discuss the Hepatitis C treatment guidelines. Dr. Richards presented a summary of the drug costs for treating hepatitis C based on diagnosis and length of treatment. The drug costs are:

Viekira® Pak (ombitasvir/paritaprevir/ritonavir/dasabuvir)	$83,318.76 to $166,637.52
Sovaldi® (sofosbuvir)	$84,000 to $336,000
Olysio® (simeprevir)	$61,929 to $123,858
Harvoni® (ledipasvir/sofosbuvir)	$63.000 to $189,000

Texas Medicaid has identified Victrelis® (boceprevir) and Viekira® Pak as their preferred agents. Victrelis® will be discontinued December 31, 2015 due to a business decision, therefore, the company is recommending not starting any new patients on this drug. Texas Medicaid has identified Harvoni®, Olysio® and Sovaldi® as non-preferred agents with the following prior authorization criteria:

- Treatment failure with preferred drugs within any subclass
- Contraindications to preferred drugs
- Allergic reaction to preferred drugs

Due to different funding sources and the use of a Group Purchasing Organization for establishing our drug contract, the Committee recommended not following the Texas Medicaid's recommendations for medication preferences.

To be eligible for treatment with the Texas Medicaid program, the patient must meet the following criteria:

- Patient is a Texas Medicaid patient greater than or equal to 18 years of age
- Patient must have the diagnosis of Chronic Hepatitis C Virus (HCV) with a confirmed genotype of 1a, 1b, 2, 3, or 4.
- Patient must have at least one negative drug screening within 30 days prior to the start of HCV treatment
- Patient with diagnosis of illicit drug use disorder must have initiated a substance use disorder treatment program at least 6 months prior to the start of HCV treatment
- Patient is not consuming alcohol
- Prescriber must be a Board Certified Gastroenterologist, Hepatologist, or Infectious Disease physician for initial approval.
    - A prescriber other than the above specialists may prescribe refills and assume responsibility and care for the patient when written consult is provided by the specialist within the last 3 months. Documentation of consult must be submitted.
- Patient with METAVIR scores 3 or 4
    - Or hepatocellular carcinoma regardless of METAVIR score
    - Or post liver transplant regardless of METAVIR score
- Patient or if applicable, patient's female partner, is not pregnant or attempting conception,
    - Patient's pregnancy status must be confirmed by a pregnancy test within 30 days prior to the start of HCV treatment
- Prescriber confirms that the patient is mentally competent and able to make appropriate decisions throughout treatment and is capable of completing therapy.
- Prescriber agrees to provide required lab results at baseline and as required to monitor therapy including but not limited to:
    - Height, weight, liver function tests, serum creatinine, creatinine clearance, hemoglobin, white blood cell count, absolute neutrophil count, and platelets.
    - HCV RNA levels at baseline, treatment weeks 4 and 12, and week 24 if applicable
    - Documentation of labs used in the calculation of METAVIR Score must be provided if requested by the patient's health care plan

The Committee suggested that the Texas Medicaid eligibility criteria be used to determine eligibility within the facilities. Dr. Muse reported that Rusk State Hospital currently has 35 patients with Hepatitis C for which 15 patients would qualify for treatment. The number of patients that meet criteria for treatment will create a financial burden for the facilities. Therefore, the Committee discussed a few possible options for funding medication cost.

- The primary goal should be to develop a statewide funding source so that all eligible Texans can receive treatment. Dr. Muse is currently working on this goal. However, it will not happen anytime soon.
- In the interim, the following strategies should be used to fund treatment:
    - The facility should look at other funding sources, such as Medicare Part D. If the patient has a Medicare Part D plan, then the medication that is on their Formulary should be used.
    - If the patient is not on a Medicare Part D plan, then a Patient Assistance Program (PAP) should be used if possible.
    - If the other two options are not available, then general revenue (GR) funding should be used

On a motion of Dr. Hall, seconded by Dr. Pittman, the recommendations to adopt the Texas Medicaid eligibility criteria, pursue statewide funding and to utilize suggested funding strategies were approved.

Quarterly Non-Formulary Drug Justification Report

For the second quarter of fiscal year 2015, all facilities reported use of non-formulary agents. The DADS facilities submitted 1,026 non-formulary requests and the DSHS facilities had 443 requests. The following were the top non-formulary agents that were prescribed:

Saccharomyces boulardii capsule (Florastor®)
Levalbuterol (Xopenex®)
Wound dressing
Meningococcal conjugate vaccine (Menactra®)
Fiber-Stat laxation solution packets
Magnesium oxide (Mag-Ox®)
Moxifloxacin (Avelox®) eye drops

In discussing the non-formulary drug purchases; the Committee suggested reviewing the following for addition to the Formulary:

Moxifloxacin (Avelox®) eye drops
Meningococcal conjugate vaccine (Menactra®)
Magnesium oxide (Mag-Ox®)

In addition, the Committee discussed reviewing the recommended vaccine guidelines to see if the drugs on the Formulary support the recommended vaccine schedule. The Committee suggested reviewing purchases of dexmethylphenidate (Focalin®).

Sectional Review for Next Meeting

The following section will be reviewed at the next meeting:

Gastrointestinal Agents
Muscle Relaxant Agents

Other Issues

The following information was shared with the Committee members:

The New York Times reports that Gilead Sciences announced that during 2014, the company sold $10.3 billion "of its new hepatitis C drug Sovaldi (sofosbuvir)," which brought the treatment "close to being the best-selling drug in the world in only its first year on the market." The Times notes, however, that the sales were "lower than they might have been," as a result of the company's "introduction of an even newer hepatitis C drug, Harvoni [ledipasvir and sofosbuvir], which recorded $2.1 billion in sales since its approval in October." Pharmacy benefits managers and insurers "are now trying to control costs by pitting Gilead against AbbVie, which introduced a hepatitis C treatment called Viekira Pak [ombitasvir, paritaprevir and ritonavir tablets; dasabuvir tablets] in December," but the Times adds that "it is not clear if they will significantly reduce overall costs for" treatment because, in some cases, "in exchange for the discounts, payers are agreeing to treat more patients," and until now "many plans have been restricting treatment to patients with more advanced liver disease."

The Pittsburgh (PA) Post-Gazette reports, "The University of Pittsburgh Graduate School of Public Health will participate in a study that could hasten the day when a patient's genetic profile, not trial and error, helps a doctor determine which medications to prescribe." Included in the "28-month, $350,000 study" will be "about 400 volunteers with mental-health disorders who are clients of NHS Human Services in Allegheny, Beaver, Dauphin and Lehigh counties." Investigators "will analyze genetic material from about half of the volunteers and use those insights to make medication adjustments aimed at optimizing drug

performance and decreasing side effects and adverse drug interactions," while the other participants, who will serve as the control group, will get "usual care."

The USA Today reports that the DOJ has announced that the US division of AstraZeneca will "pay the federal government $7.9 million to settle allegations" that the drug maker paid pharmacy benefit manager Medco Health Solutions a kickback to keep the "sole and exclusive" status of heartburn treatment Nexium (esomeprazole) on the formulary. AstraZeneca LP purportedly "gave Medco price breaks on other drugs the company marketed," including Prilosec (omeprazole), "another heartburn drug, as well as" Toprol XL (metoprolol succinate) and Plendil (felodipine), high blood pressure treatments. "Despite the settlement," the paper adds, "AstraZeneca LP denied the government allegations," saying acceptance of the settlement is "in the best interest of the company...to move forward with our business of discovering and developing important, life-changing medicines — while avoiding the delay, uncertainty, and expense of protracted litigation."

The Washington Post "Wonkblog" reported, in continuing coverage, on John Oliver's criticism of the pharmaceutical industry in the US, in which Oliver "mentioned that nine out of 10 big pharmaceutical companies spend more on marketing than on research." Johnson & Johnson appears to be the "biggest spender," having "shelled out $17.5 billion on sales and marketing in 2013, compared with $8.2 billion for R&D." Oliver also "pointed out drug companies spent more than $3 billion a year marketing" to consumers in the US in 2012 versus "an estimated $24 billion marketing directly to health care professionals."

The Wall Street Journal "Pharmalot" blog reports that Johnson & Johnson (J&J) has been ordered to pay $2.5 million in damages relating to its failure to warn users properly of the fact that its antipsychotic treatment Risperdal (risperidone) could cause gynecomastia, the abnormal development of breasts in males. Notably, former FDA Commissioner David Kessler served as an expert witness for the prosecution and testified that the pharmaceutical maker was aware of the risks associated with Risperdal, but failed to display the data showing the extent to which kids could develop gynecomastia.

From CredibleMeds:

- When CredibleMeds' QT drugs list was launched in 2000, fosphenytoin (Cerebyx®, Prodilantin®) was placed on the list of drugs with Possible Risk of TdP. However, there was only minimal evidence of QT prolongation and since then; no credible evidence of QT prolongation and/or TdP has been subsequently found. Therefore, we **have removed fosphenytoin** from the Possible Risk List and from the list of Drugs to Avoid for patients with congenital Long QT Syndrome (LQTS).
- We also reviewed ciprofloxacin (Cipro® and other brands) and fluconazole (Diflucan® and other brands) and, based on our analysis of the available evidence, we have moved these drugs from the Conditional Risk List to the list of drugs with **Known Risk of TdP**.
- Furthermore, we reviewed the available evidence for propofol (Diprivan®, Propoven® and other brands) and have added propofol the list of drugs with **Known Risk of TdP**.
- Note that ciprofloxacin, fluconazole and propofol are also on the list of drugs to Avoid for patients with congenital LQTS.
- We have found convincing evidence that donepezil (Aricept®), a drug prescribed for dementia (Alzheimer's Disease), is associated with Torsades de Pointes (TdP). We have added it to the list with **Known Risk of TdP**.
- We also added cilostazol (Pletal®), a drug for treatment of intermittent claudication, to the list with **Known Risk of TdP**.
- Our review of the diuretic torsemide (Demadex® and other brands) found that, like furosemide (Lasix®), it can prolong QT by causing low serum magnesium and/or low serum potassium, conditions that are associated with TdP. Therefore is has been added to the list with **Conditional Risk of TdP**.
- Atomoxetine (Strattera®) is an adrenergic drug for ADHD that is now listed on the **Drugs to be Avoided** in patients with congenital long QT syndrome. We have found convincing evidence that it also has the ability to prolong QT interval and have added it to the list of drugs with **Possible Risk of TdP**.

- Note that donepezil, cilostazol, torsemide, and atomoxetine the drugs listed above are also on the list of **Drugs to Avoid for patients with congenital LQTS**.

Modern Healthcare reports, "Internists, family medicine physicians, psychiatrists and neurologists wrote more than 80% of the prescriptions for antipsychotics for older adults with dementia in 2012, according to a report calling for expanded federal efforts to curb use of the drugs." The Government Accountability Office report said that "though several initiatives have addressed overuse of the medications among nursing home patients who do not have a diagnosis of psychosis, no actions have specifically been directed to other settings."

The Detroit Free Press reports that a study published online March 18 in JAMA Psychiatry and funded by the National Institute of Mental Health and the National Institute on Aging, "strengthens the case against the practice of prescribing antipsychotic drugs to treat delusions, hallucinations, agitation and aggression – symptoms of dementia, including of Alzheimer's disease." Researchers arrived at that conclusion after examining "medical data of more than 91,000 veterans over 65." The article also points out that the FDA "warns consumers of serious risk of side effects of" antipsychotics when used in patients with dementia.

Amy Robach reported on ABC World News on "what may be a new weapon in a fight against Alzheimer's." A new treatment from Biogen Idec is "showing signs that it could decrease the rate of cognitive decline in those battling the disease." ABC' News chief medical editor Richard Besser, MD, said the positive results, though early, "are very encouraging."

The Chicago Tribune reports on the challenges surrounding the naming of some medicines. "With thousands of drugs on the market, the No. 1 reason drug names are rejected" by the FDA is that the agency "doesn't want names to be too similar when prescriptions are filled," citing Brannon Cashion, global president of branding firm Addison Whitney. Some names require them to have a "punch," according to the piece. Commenting on the name of recently approved biosimilar Zarxio (filgrastim-Sandoz), Cashion said, "The name has a very positive, fast, strong sound," adding, "It's punchy."

Reuters reports that a paper published online March 23 in the journal Pediatrics suggests that physicians advise adolescents taking selective serotonin reuptake inhibitor antidepressants for anxiety or depression of potential sexual side effects. In adults, SSRI antidepressants can result in sexual side effects greater than half the time, and teenagers may experience them at a similar rate.

Wyatt Andrews of CBS Evening News reported on a "groundbreaking clinical trial testing whether a drug called solanezumab could slow down or even prevent Alzheimer's disease." The trial, "called the A4 Alzheimer's' study," is "an ambitious international trial in which 60 hospitals are looking for 1,000 patients" who "have no sign of memory loss yet," but have undergone brain scans that have "suggested they will get Alzheimer's in the future." The hope is that solanezumab "destroys the amyloid" plaque, which physicians "believe is what kills off brain cells," before the amyloid builds up. Reisa Sperling, MD, MMSc, a Harvard University physician and the project director of the study, told CBS News, "If we can treat the amyloid plaque buildup early enough, we can prevent memory loss. That's really a new way of thinking about Alzheimer's disease."

Medscape reported that an experimental antipsychotic, ITI-007, showed positive results in a phase 2 trial "as an effective agent in the treatment of schizophrenia." The treatment "demonstrated reduced motor and metabolic side effects compared with the antipsychotic risperidone," and "importantly, both the group receiving 60 mg" of the medicine "and the group receiving 120 mg showed significantly lower levels of metabolic measures that are increased with the popular antipsychotic...risperidone, including insulin, glucose, triglyceride, total cholesterol, and LDL cholesterol levels."

The Daily Mail (UK) reports that a "new designer drug" called Flakka is "spreading across Florida." The drug, which "can be injected, snorted, smoked, swallowed or taken with other substances like marijuana," is "usually made from the chemical alpha-PVP," the same type of chemical used to manufacture bath salts.

Medscape reports that the results of a Phase 3 randomized clinical study published this week in JAMA Psychiatry and presented March 31 at the 15th Annual Congress on Schizophrenia Research reveal that a three-month "formulation of the antipsychotic paliperidone (Invega, Janssen Pharmaceuticals, Inc) significantly delays relapse in schizophrenia patients with no increase in adverse events (AEs)." The study "involved 506 patients."

HealthDay reports that a study published online April 6 in the journal Pediatrics associates the anti-epilepsy medication topiramate with "increased odds of eating disorders in some teens." The medicine was approved last year for use in adolescents as a migraine preventive. In seven cases involving girls aged 13 to 18; researchers found that weight loss associated with use of the medication "can trigger symptoms of an eating disorder."

Medscape reported that research presented March 30 at the 15th International Congress on Schizophrenia Research suggests that encenicline (EVP-6124), a "novel α-7 nicotinic acetylcholine receptor partial agonist," showed "significant cognitive improvements" for patients with schizophrenia in a "phase 2, multicenter, double-blind study." In the study, 319 patients "with a diagnosis of schizophrenia for three or more years were randomly assigned 1:1:1 to receive encenicline in doses of 0.27 mg or 0.9 mg once daily or placebo" over a 12-week period. The improvements were seen "in the encenicline groups in both dose groups at various measures."

Next Meeting Date

The next meeting was scheduled for July 24, 2015.

At the next meeting, the Committee will review weight vs. waist circumference for determining/monitoring Metabolic Syndrome.

Adjourn

There being no further business, the meeting was adjourned at 1:50 p.m.

William Race, M.D.
Approved: _____
William Race, M.D., Chairman

Attachments
Attachment A – Psychotropic Monitoring Guidelines – Lab Summary
Attachment B – Psychotropic Agents Sectional Review
Attachment C – Select Medication Brief Overview

Minutes Prepared by:
Ann L. Richards, Pharm.D., BCPP